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EXAMINER	
CANELLA, KAREN A	
ART UNIT	**PAPER NUMBER**
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/961,407	TORRANCE ET AL.	
	Examiner	Art Unit	
	Karen A Canella	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) 1-52 is/are pending in the application.

4a) Of the above claim(s) 21-52 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) 1-20 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date Mar 11, 2002.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Acknowledgment is made of applicants election of Group I, drawn to isogenic cell lines. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP ' 818.03(a)).

Claims 1-52 are pending. Claims 21-52, drawn to non-elected inventions, are withdrawn form consideration. Claims 1-20 are examined on the merits.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-17 are drawn to a genus of isogenic cell lines comprising a "gene of interest". The claims are relying upon the identity of said gene of interest in order to characterize the claimed cell lines. The genes of interest encompass any allele of any gene, including mutant, and null alleles. the specification describes the isogenic cell lines wherein the first cell is heterozygous comprising a wt Ras gene and a mutant Ras gene, and wherein the second cell is hemizygous for wild-type Ras. the art recognizes the sequences of numerous mutations of Ras which are found in human tumor specimens and which confer a tumorigenic phenotype when transfected into host cells. The genus comprising "genes of interest" encompasses any gene beyond the scope of the described Ras genes, and includes tumor suppressor genes, and genes not related to cancer cells or the tumorigenic phenotype. the description of the Ras oncogenes does not describe the genus of "genes of interest" on which the instant claims for isogenic cell

lines depend because the genus is highly variant encompassing genes, such as tumor suppressor genes, which differ from the Ras oncogenes in that said genes are recessive and not dominant-negative, in addition to genes which are not related to cancer cells or the tumorigenic phenotype.

Further, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." Id. At 1567, 43 USPQ2d at 1405. The court also stated that

a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that "the written description requirement can be met by 'show[ing] that an invention is complete by

disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. " Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

In the instant claims, the genus is described only as genes of interest are not limited either by function or by structure.

The inventions at issue in Lilly and Enzo were DNA constructs per se, the holdings of those cases are also applicable to claims such as those at issue here. A cell line comprising a gene wherein the gene is not adequately described a cannot itself be adequately described..

Thus, the instant specification may provide an adequate written description of isogenic cell lines comprising mutant Ras genes, per Lilly if the claims were limited to such. however, at present the claims have no limitation as to functional attributes, as per Enzo, nor does the specification describe a number of specific examples that would adequately describe the highly variant genus. Thus, one of skill in the art would reasonably conclude that applicant was not in possession of the claimed genus of isogenic cells because applicant did not adequately describe the genus of "genes of interest".

Claims 1-17 are unpatentable over Waldman (US 2002/0132340, priority to 60/274,393) in view of Kain (Drug discovery today, 1999, vol. 4, pp. 304-312).

If a copy of a provisional application listed on the bottom portion of the accompanying Notice of References Cited (PTO-892) form is not included with this Office action and the PTO-892 has been annotated to indicate that the copy was not readily available, it is because the copy could not be readily obtained when the Office action was mailed. Should applicant desire a copy of such a provisional application, applicant should promptly request the copy from the Office of Public Records (OPR) in accordance with 37 CFR 1.14(a)(1)(iv), paying the required fee under 37 CFR 1.19(b)(1). If a copy is ordered from OPR, the shortened statutory period for reply to this Office action will not be reset under MPEP § 710.06 unless applicant can demonstrate a substantial delay by the Office in fulfilling the order for the copy of the provisional application. Where the applicant has been notified on the PTO-892 that a copy of the provisional application

is not readily available, the provision of MPEP § 707.05(a) that a copy of the cited reference will be automatically furnished without charge does not apply.

Claim 1 is drawn to a pair of cells comprising a first cell and a second cell wherein the first cell and the second cell are isogenic but for a gene of interest and a gene encoding a fluorescent protein; wherein the first cell comprises a gene that encodes a first fluorescence protein having an absorption spectrum and a first emission spectrum; wherein the second cell comprises a gene that encodes a second fluorescent protein having a second absorption spectrum and a second emission spectrum, and wherein either the first and second absorption spectra are not identical and/or the first and second emission spectra are not identical. claim 2 embodies the pair of cells of claim 1 wherein the first and second absorption spectra are not identical and the first and second emission spectrum are not identical. Claim 3 embodies the pair of cells of claim 1 wherein the cells are contained within the same undivided container. Claim 4 embodies the pair of cells of claim 1 wherein the first cell is homozygously wild-type for the gene of interest and wherein the second cells is homozygoulsy mutant for the gene of interest. Claim 5 embodies the pair of cells of claim 1 wherein the gene of interest in the second cell is homozygously deleted. Claim 6 embodies the pair of cells of claim 1 wherein the first cell comprises two wild-type alleles of the gene of interest, and wherein the second cell comprises a wild-type allele and a mutant allele of the gene of interest wherein the mutant allele is dominant. Claim 7 embodies the pair of cells of claim 1 wherein the gene of interest is an oncogene and the first cell is homozygous for a mutant allele of the oncogene and wherein the second cell comprises a homozygous deletion of the mutant oncogene. Claim 8 embodies the pair of cells of claim 1 wherein the first cell expresses the gene of interest and wherein the second cell does not express the gene of interest. Claim 9 embodies the pair of cells of claim 1 wherein the first cell comprises a wild-type allele and a mutant allele of the gene of interest and the second cell is hemizygous for the wild-type allele of interest. Claim 10 embodies the pair of cells of claim 1 wherein the first cell expresses a protein encoded by the gene of interest and wherein the second cell does not express a protein encoded by the gene of interest. Claims 11 and 12 embody the pair of cells of claim 1 wherein the first and second cells are mammalian cells and human cells, respectively. Claims 15 and 16 specify that the cells of claim 1 are HCT116 cells and DLD-1 cells, respectively. Claim 17 embodies the pair of cells of claim 1 wherein the first and second

fluorescent protein are selected from the group consisting of green , red, blue, yellow and cyan fluorescence protein. Claim 13 embodies the pair of cell of claim 1 wherein the cells are cancer cells. Claim 14 embodies the pair of cells of claim 13 wherein the cancer cells are selected from the group consisting of colon tumor cells and breast tumor cells.

Waldman teaches a pair of isogenic cell lines comprising beta-catenin, wherein said cells are heterozygous for a wild-type and a mutant beta catenin gene, or hemizygous for wild-type beta-catenin, hemizygous for mutant beta-catenin, homozygous for wild-type beta catenin and homozygous for mutant beta-catenin [0010-0012]. It is noted that the descriptions of first and second cells by Waldman et al is not limiting and done only for descriptive purposes [0032]. Waldman teaches that the pair of cells can include cells which are null for beta-catenin expression, thus fulfilling the specific embodiment of claims 8 and 10, drawn to the second cell not expressing the gene of interest or the protein of the gene of interest. Waldman defines "hemizygous" as cells containing only a single copy of the beta-catenin gene or a single functional beta-catenin gene [0034]. Waldman teaches a method wherein a therapeutic agent is identified that allows for the selective killing of cells expressing mutant beta-catenin but not wild-type beta catenin comprising contacting an isogenic set of cells with a test agent and identifying an agent that allows for the selective killing [0020]. Waldman teaches that the set of isogenic cell lines can be prepared from human colon carcinoma cells of the HCT-116 cell line and the DLD-1 cell line [0038-0039], thus fulfilling the specific embodiments of claims 11-16. Waldman teaches that the isogenic cell line disclosed represents an improvement over the prior art because they make possible a method for distinguishing between a compounds which selectively kills cancer cells having mutant rather than wild-type beta catenin and compounds which kill cells but re not selective for cells having mutant rather than wild-type beta catenin [0029]. Waldman teaches that a polypeptide expressed from a polynucleotide of a recombinant nucleic acid can confer a detectable phenotype on the cell, and the detectable phenotype can be used as a surrogate for increased resistance or susceptibility to a toxic agent, and that the detectable phenotype can include the production of a fluorescent signal [0047]. Waldman teaches that red, green and cyan fluorescent proteins as specific embodiments of fluorescent proteins which can act as reporter molecules [0048]. Waldman does not teach a fluorescent gene

incorporated into the first cell and the second cell wherein said fluorescence genes encoded proteins having different emission and excitation spectra.

Kain teaches the use of multicolored florescent proteins for more detailed information regarding cellular processes 9page 310, first column, lines 3-5) and teaches the use of fluorescent proteins are reporter for transcription (page 306, second column). Kain teaches various fluorescent proteins which have different excitation and emission maxima (page 306, Table 1) thus fulfilling the limitations of claims 1 and 17. Kain teaches that various combinations of the disclosed fluorescent proteins have been used to quantify mixed cell populations (page 306, first column, lines 29-32)

It would have been prima facie obvious to one of skill in the art at the time the invention was made to make the isogenic cells expressing the beta catenin wild type and mutant alleles, wherein said mutant alleles were fused to a fluorescent protein and wherein a wild-type allele was fused to a different fluorescent protein than the mutant allele. One of skill in the art would be motivated to do so in order to use the color of the fluorescent protein as a detectable phenotype of the cell in order to measure the effects of toxic agent on said cell as taught by Waldman et al. One of skill in the art would be motivated to do so because Waldman suggests the use of a fluorescent signal as a detectable phenotype. One of skill in the art would known that a mixture of cells expressing wild type and mutant alleles of beta catenin can be more effectively assayed in a screen if the control wild type cells are exposed to the exact same conditions of the assay as the cells containing mutant, truncated or otherwise abnormal alleles of beta catenin and that co-culture would enable the cells to be subject to the same microenvironment. One of skill in the art would know that in order to discern between a signal from a mutant allele and a signal from a wild-type allele, a different color of fluorescent label should be used which ideally would have a different excitation maximum and a different emission spectrum so that spectra from the mutant allele can be generated from a separate excitation wavelength than the wild-type allele and the subsequent emission spectrum can be measured.

Claims 1-3, 11-20 are unpatentable over Shirasawa et al (Science, 1993, vol. 260, pp. 85-88) in view of Vande Woude et al (U.S. 5,645,988)and Kain (Drug discovery today, 1999, vol. 4, pp. 304-312).

The specific embodiments of claims 1-3 and 11-20 are set forth above.

Claim 18 embodies the method of claim 1 wherein the gene of interest is Ras and wherein the Ras genotype of the first cell is c-Ki-Ras (Wt/Mut), and wherein the Ras genotype f the second cell is c-Ki-Ras(WT/Null).

Claim 19 is drawn to a pair of cells comprising a first cell wherein the Ras genotype of the first cell is c-Ki-Ras (WT/mut) and wherein the first cell comprises a first gene that encodes a first fluorescent protein having a first absorption spectrum and a first emission spectrum and a second cell wherein the Ras genotype of the second cell is c-Ki-Ras(Wt/null) wherein the second cell comprises a second gene that encodes a second fluorescent protein having a second absorption spectrum and a second emission spectrum that is nor identical to the first emission spectrum, wherein said first and said second cells are isogenic but for the Ras gene, and the gene encoding a fluorescent protein. Claim 20 embodies the pair of cells of claim 19 wherein the first fluorescent protein is blue and the second fluorescent protein is yellow fluorescent protein..

Shirasawa et al teach that point mutations which activate wild-type ki-Ras to oncogenic Ki-Ras are present in about 50% of human colorectal tumors (abstract). Shirasawa et al teach the targeting of the mutant ki-Ras gene for a homologous recombination event with a vector having a interrupted Ras gene sequence. Shirasawa et al teach that for DLD-1 colon cancer cells, three of the clones were disrupted at the mutant allele and four were disrupted at the normal allele (page 85, third column, lines 27-31) and in HCT-116 cells three of the clones were disrupted at the mutant K-ras allele and five were disrupted at the normal K-Ras allele (page 87, first column, lines 6-11). Thus, the clones which were disrupted at the mutant K-ras allele are the same as the c-Ki-Ras (WT/null) genotype of the second cell and the starting DLD-1 and HCT-116 cells are Ki-Ras (WT/mut). Shirasawa et al teach that the only distinction between the parental cell lines and the cell lines comprising disrupted mutant K-ras alleles is the expression of the mutated K-ras genes. Shirasawa et al do not teach the isogenic cells which additionally express two fluorescent proteins which differ by emission spectrum and excitation spectrum.

Wander Woude et al teach cancer cells derived from the same type of biological material wherein the cancer cells differ as to the presence of a particular DNA sequence (column 11, lines 27-30) wherein the preferred DNA sequence is K-ras-2 which has been activated by a mutation in the 12th, 16th or 61st codon (column 12, lines 1-4). Vander woude et al teach the desirability of selecting drugs which specifically target oncogenes (column 5, lines 9-14, column 8, lines 57-65) which includes Ras oncogenes (column 14, lines 28-32). Wander woude et al do not teach pairs of isogenic cells.

Kain teaches the use of multicolored florescent proteins for more detailed information regarding cellular processes 9page 310, first column, lines 3-5) and teaches the use of fluorescent proteins are reporter for transcription (page 306, second column). Kain teaches various fluorescent proteins which have different excitation and emission maxima (page 306, Table 1) thus fulfilling the limitations of claims 1 and 17. Kain teaches that various combinations of the disclosed fluorescent proteins have been used to quantify mixed cell populations (page 306, first column, lines 29-32).

It would have been prima facie obvious to one of skill in the art at the time the invention was made to make the isogenic cells as taught by Shirasawa et al with the exception that the isogenic cells included a gene encoding a first fluorescent protein attached to the mutant ras allele and a second fluorescent protein attached to the disrupted ras allele, wherein the first fluorescent protein is blue and the second fluorescent protein is yellow One of skill in the art would be motivated to do so in order to use the color of the fluorescent protein as a detectable phenotype of the cell in order to measure the effects of toxic agent on cell which comprise the oncogenic Ras mutations as taught by Wander woude et al. One of skill in the art would known that a mixture of cells expressing the activated oncogenic ki-Ras protein and the disrupted ki-Ras protein can be more effectively assayed in a screen if both the first and the second cells are exposed to the exact same conditions of the assay which would be fulfilled by the co-culture of said cells within the same undivided culture dish. One of skill in the art would know that in order to discern between a signal from a mutant allele and a signal from a wild-type allele, a different color of fluorescent label should be used which ideally would have a different excitation maximum and a different emission spectrum so that spectra from the mutant allele can be generated from a separate excitation wavelength than the wild-type allele and the

subsequent emission spectrum can be measured. One of skill in the art would know that the greater the separation between the excitation maxima of the first and second fluorescent proteins, the greater the probability that a fluorescent protein emission can be observed separately for each of the first and second fluorescent proteins. Based on this reasoning, it would have been obvious to select EBFP (blue) having an excitation maximum of 380 nm and EYFB (yellow) having an excitation maximum of 513 nm, thus fulfilling the specific embodiment of claim 20.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (571) 272-0828. The examiner can normally be reached on Monday through Friday from 9 am to 6:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached on (571) 272-0871. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to Customer Service at 703-308-4357.

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02/22/04

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